PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF HAIR LOSS

The present invention relates to a pharmaceutical composition for preventing or arresting scalp hair loss and/or promoting scalp hair growth and in particular to a composition for topical application.

The present invention provides a pharmaceutical composition for preventing or arresting scalp hair loss and/or promoting scalp hair growth comprising an anti-androgen, an oestrogen and a thyroid hormone. The compositions according to the invention may in general be used either by male or female patients.

An antiandrogen is herein defined as an agent which suppresses the secretion of androgens from either the adrenal glands or testes or ovaries either by suppressing pituitary gonadotrophin or ACTH/secretion or reducing androgen secretion directly from the adrenal glands, ovaries or testes themselves, or is effective locally within the tissues by either displacing androgen from its tissue receptor or competing with its action, or which has an opposite action to androgens (e.g. oestrogen) or impairs the conversion of an androgen substrate to its

biologically more active form as testosterone or dihydrotestosterone (e.g. 5 alpha reductase inhibitors such as progesterone), or inhibits in any other way the synthesis and/or the secretion and/or the action of androgens.

The composition according to this invention includes at least one oestrogen, e.g. oestradiol or a pharmaceutically suitable derivative thereof such as oestradiol benzoate, or ethinyloestradiol, in combination with at least one non-oestrogenic anti-androgen such as a progesterone-like compound e.g. medroxyprogesterone acetate or a similarily pharmaceutically acceptable derivative of medroxyprogesterone. Another suitable non-oestrogenic anti-androgen for use in the compositions according to this invention would be cyproterone acetate or another pharmaceutically suitable derivative of cyproterone. Although cyproterone acetate and medroxyprogesterone acetate are the preferred anti-androgens for use in the compositions according to the invention, other antiandrogens having a progesterone-like activity may suitably be employed. These include allyloestrenol,gestronol (e.g. as the hexanoate), dydrogesterone, norgestrel, levonorgestrel, norethisterone, hydroxyprogesterone (e.g. as the hexanoate), progesterone itself, cimetidine or azelaic acid.

The thyroid hormone present in the preparations according to the invention is preferably triiodothyronine or a pharmaceutically suitable derivative or precursor therefor. Alternatively, the thyroid hormone may be thyroxine. Thyroxine exerts most, if not all, of its biological activity by conversion in the body to triiodothyronine.

The pharmaceutical compositions according to the invention are preferably formulated as creams, gels, ointments, pastes or lotions for topical application. For this purpose, any suitable carrier system normally employed in the preparation of such pharmaceutical compositions may be employed. For instance, the ingredients may be dispersed in an ointment base such as "unguentum merck" or dissolved in a lotion base such as aqueous ethanol. Systemic treatment using the oral or parenteral routes is also possible.

The compositions may suitably provide a concentration of anti-androgen of at least 0.01 percent by weight and a concentration of thyroid hormone suitable to provide from 2 - 200μg per 3ml. 3 ml is a typical single dose.

More preferably, the compositions may provide from 0.05 - 0.4% by weight anti-androgen, most preferably about 0.1% of each of an oestrogenic anti-androgen such as oestradiol benzoate and a non-oestrogenic anti-androgen such as medroxyprogesterone acetate.

Most preferably, the composition provides about 20 μg per 3ml dosage of the composition of triiodothyronine.

Such a formulation is suitably applied about twice a day to the areas in which it is desired to prevent or arrest scalp hair loss and/or promote scalp hair growth.

The effectiveness of the compositions of the present invention may be enhanced by including therein other substances which are known to promote or suspected of being able to promote scalp hair growth. Examples of such substances are vasodilators, alpha-adrenergic blockers, anabolic growth-promoting agents, and "second messenger" hormone effector enzymes.

The following examples illustrate the present invention, and tentative conclusions have been drawn from the results so far achieved. It must be recognised, however, that, although for the most part human beings react in similar ways to the same drugs, individuals vary considerably as to their sensitivity to a particular drug. Hence the lower limits suggested herebelow for the effective levels of the components must be regarded with caution.

Clinical Studies

1. Effect of a Topical antiandrogen preparation on hair growth in four normal men compared with six untreated (control) men over one year (Trichogen I - Table 1; Figures 1, 2, 3 and 4)

Clinical studies using the application of a topical antiandrogen preparation were carried out in male patients and the response in hair growth compared with an untreated control group using the technique of the Unit Area Trichogram as previously described (The Unit Area Trichogram in the Assessment of Androgen-dependent Alopecia. Rushton H, James K C, Mortimer C H. British Journal of Dermatology: (1983), 109, 429-437)

Four male patients aged between 27 years to 54 years with a history of common baldness of 6 to 24 years duration had Unit Area Trichograms carried out before and after 12 months of applying a topical antiandrogen preparation comprising:

Trichogen I

Oestradiol Benzoate 0.1%
Medroxyprogesterone Acetate 0.1%
3, 3¯ 5 Triiodo-L-Thyronine Free Acid 20ug per 3ml of solution

The preparation, total volume 3ml, was applied twice daily to several sites in divided quantities to the frontal and vertex areas of the scalp.

Six male volunteers aged between 21 to 34 years with a history of common baldness of 1½ to 6 years duration formed the control group and did not receive any treatment.

Unit Area Trichograms in the occipital area were performed in 3 of the treatment group and 5 of the control group. The shaded area in the Figures identifies the normal range for the measurements shown and the individual symbols correspond to the same subjects, set out in Table 1.

All four men in the treatment group had an increase in frontal total hair density (hairs/cm2) during 12 months of therapy. None of the men in the control group had an increase in frontal total hair density during 12 months (Figure 1).

Three of the treated men showed an increase in frontal meaningful hair density (number of hairs greater than 40um in diameter/cm2; it is these hairs which have the capability of growing to full length) during 12 months of therapy. In one patient the increase in frontal meaningful density was not significant. No man in the control group showed an increase in meaningful hair density during 12 months (Figure 2).

In each of the three treated men in whom occipital total hair density was measured there was an increase during 12 months of treatment. None of the five men in whom occipital total hair density was measured in the control group showed an increase in occipital total hair density during 12 months (Figure 3).

Two of the three men in the treatment group showed an increase in occipital meaningful hair density (number of hairs greater than 40um in diameter/cm2; it is these hairs which have the capability of growing to full length) during 12 months of therapy whereas one patient remained unchanged. None of the five men in the control group showed an increase in occipital meaningful hair density during 12 months (Figure 4).

Conclusion

The application of the above preparation Trichogen I, results in the arrest of the balding process with an increase in total hair density and meaningful hair density in both the frontal and occipital areas during 12 months of treatment. It is evident that there is cross-circulation with the effective dispersal of local antiandrogen activity between the frontal and occipital areas.

2. Effect of a topical antiandrogen preparation plus topical arterial vasodilator on hair growth in a single patient (Trichogen II - Figure 5)

A male patient aged 24 years with hair fall of 2 years duration with a clinical picture of male pattern baldness had the following results:

Before treatment:

Hormonal Profile:

Testosterone	20.8	nmol/L	(n 10-32)
SHBG	31.0	nmol/L	(n 18-40)
Oestradiol	125.0	pmol/L	(n 50-180)
Dihydrotestosterone	1.5	nmol/L	(n 0.7-2.7)

Semen Analysis

*Total Count	8 millions	(n greater than 80 millions)
*Motility	50%	(n greater than 60%)
Abnormal forms	10%	(n up to 25%)

The patient had previously had an undescended testis replaced in the scrotum (orchidopexy) in 1969. This condition is frequently associated with a reduced sperm count but otherwise normal testicular function with respect to testosterone secretion and potency.

Unit Area Trichogram:	Frontal	Occipital
Total Hair Density (Hairs/cm2)	263 (n 256-393)	251 (n 261-356)
Meaningful Hair Density (Hairs greater than 40um in diameter/cm2)	215 (n 232-340)	246 (n 213-317)

After 6 months of Systemic Antiandrogen Treatment

Initially he began treatment with Medroxyprogesterone Acetate starting with 5mg daily increasing to 40mg daily at 6 months.

At this time the following hormone results were obtained:

Testosterone	27.0	nmol/L	(n 10-32)
SHBG	36.0	nmol/L	(n 18-40)
Oestradiol	171.0	pmol/L	(n 50-180)
Dihydrotestosterone	2.1	nmol/L	(n 0.7-2.7)

Semen Analysis

*Total Count	5 millions	(n greater than 80 millions)
*Motility	10%	(n greater than 60%)
*Abnormal forms	35%	(n up to 25%)

Despite receiving Medroxyprogesterone Acetate orally, the patients plasma testosterone level was not suppressed and the Unit Area Trichogram was as follows:

Unit Area Trichogram:	Frontal	Occipital
Total Hair Density (Hairs/cm2)	248 (n 256-393)	280 (n 261-356)
Meaningful Hair Density (Hairs greater than 40um in diameter/cm2)	179 (n 232-340)	271 (n 213-317)

i.e. Worse in the frontal area.

The following measurements were then carried out:

*Dehydroepiandrosterone Sulphate (DHEAS)	9.4 umol/L	(n 5-9)
*17 Alpha Hydroxyprogesterone	10.1 nmol/L	(n 0.6-6.0)
Androstenedione	4.9 nmol/L	(n 3.1-10.0)

These results indicated that the patient had not significantly suppressed total testosterone secretion while on Medroxyprogesterone Acetate and the elevated DHEAS and 17 alpha hydroxyprogesterone levels were consistent with an adrenal origin for the hormones. There had been a deterioration in the patients Unit Area Trichogram in the frontal area. At this stage it was decided to maintain the patients Medroxyprogesterone Acetate intake but to add topical antiandrogen therapy as:

Trichogen II

Medroxyprogesterone Acetate 0.2%.
Oestradiol Benzoate 0.2%.
3,3¯, 5 Triiodo-L-Thyronine Free Acid in super-saturated solution.
3,3¯, 5 Triiodo-D-Thyronine Free Acid in super-saturated solution.
Phentolamine Mesylate 0.1% (as Rogitine, Ciba).

The patient applied 1ml of the above preparation twice daily to the scalp.

After 6 months of the same dose of systemic Medroxyprogesterone Acetate plus Trichogen II the following results were obtained:

Testosterone	31.0	nmol/L	(n 10.32)
SHBG	19.0	nmol/L	(n 18-40)
Oestradiol	125.0	pmol/L	(n 50-180)
Dihydrotestosterone	2.1	nmol/L	(n 0.7-2.7)
*DHEAS	10.0	umol/L	(n 5-9)
*17 Hydroxyprogesterone	6.7	nmol/L	(n 0.6-6.0)
Androstenedione	5.8	nmol/L	(n 3.1-10.0)

Semen Analysis

*Total Count	16.8 millions	(n greater than 80 millions)
Motility	65%	(n greater than 60%)
Abnormal forms	10%	(n up to 25%)

The Unit Area Trichogram showed:

Unit Area Trichogram:	Frontal	Occipital
Total Hair Density (Hairs/cm2)	307 (n 256-393)	282 (n 261-356)
Meaningful Hair Density (Hairs greater than 40um in diameter/cm2)	248 (n 232-340)	263 (n 213-317)

The above Unit Area Trichogram results are shown in diagramatic form (Figure 5).

The above results show that in this patient with male pattern baldness Medroxyprogesterone Acetate up to 40mg per day while being effective in most men to suppress pituitary LH and FSH secretion was not effective in reducing this patients circulating testosterone levels since in addition to androgens of testicular origin there was evidence of an adrenal source for these. During the first 6 months of systemic Medroxyprogesterone Acetate treatment there was no significant reduction in circulating androgen levels and the patients frontal hair density studies showed a deterioration. There was an improvement in the occipital region. This is generally to be expected since this area is more resistant to the balding process and recovers more quickly than the frontal area. It is probable that the inhibition of 5 alpha reductase activity with decreased conversion of testosterone to dihydrotestosterone in the scalp of the occipital area was sufficient to allow new hair growth without suppression of circulating androgen levels.

After a further 6 months of systemic Medroxyprogesterone Acetate treatment circulating androgen levels were still not reduced and in fact higher than the basal levels. However, during this time, the addition of Trichogen II resulted in new hair growth in the frontal area. This must have been due to the local inhibition of androgen activity in the scalp by local absorption of Trichogen II.

3. Effect of a Topical Antiandrogen Preparation plus cyclic AMP/ATP/ Phosphodiesterase Inhibitor on hair growth in a single male patient (Trichogen III) - Figures 6, 7

It is recognised that many hormones including steroids act by the activation of the cyclic AMP mechanism. In this process hormones interact with specific receptors on the cell membrane. This results in the activation of membrane bound adenylate cyclase which enhances the conversion of ATP (Adenosine Triphosphate) to cyclic AMP (cyclic adenosine 3, 5, monophosphate). Cyclic AMP is known as the ubiquitous second messenger since it is able to relay information derived from numerous substances binding at the cell surface. The cyclic AMP then activates a variety of protein kinases by combining with the regulatory sub-group of the enzyme which is then dissociated from the catalytic sub-group. The catalytic sub-unit then catalyses the phosphorylation of certain key proteins, usually enzymes, which then leads to the action of the original hormone which presented at the cell membrane. This mechanism also results in the elaboration of various proteins which may themselves be hormones or comprise specific tissue e.g. muscle tissue, nerve tissue, hair. The process may also be modified by the availability of calcium, cyclic GMP (cyclic guanosine 3, 5 monophosphate) or other enzyme systems. Other hormones may achieve their action by entering the cell directly to bind with specific cytoplasmic receptors which are then modified and transport the hormone receptor complex into the nucleus where specific genes are activated to produce the end result. These mechanisms are shown diagramatically in Figure 6. Cyclic AMP is inactivated by phosphodiesterase. The latter enzyme itself can be inactivated by theophylline and caffeine thereby leading to an increase in the cyclic AMP concentration in certain tissues.

In order to enhance the effects of the topical antiandrogen preparation a further solution was made up to contain:

Trichogen III

Oestradiol Benzoate 0.2%
Medroxyprogesterone Acetate 0.2%
3, 5" Triiodo-L-Thyronine Free Acid in super-saturated solution
Phentolamine Mesylate 0.04%
Cyclic AMP Free Acid 0.1%
Cyclic AMP Sodium 0.05%
ATP Magnesium 0.1%
Choline Theophyllinate 0.05%

A 25 year old man with common baldness had previously been treated with Medroxyprogesterone Acetate increasing to 40mg daily until 68 weeks when the dose was reduced to 20mg daily, then after 72 weeks to 10mg daily until 78 weeks when treatment was stopped. The results of the Unit Area Trichogram are shown in Figure 7. After 26 weeks without systemic Medroxyprogesterone Acetate the patient showed a decrease in total hair density in the frontal site. After 52 weeks without treatment there was also a marked decrease in meaningful hair density in the frontal site. The occipital region remained unchanged. Instead of re-introducing systemic Medroxyprogesterone Acetate the patient began treatment with the above preparation 2ml applied 4 times daily to the scalp in the frontal and vertex areas.

After 26 weeks of topical treatment with **Trichogen III** there was an increase in total hair density in the frontal site from 197 hairs/cm2 to 233 hairs/cm2. There was also an increase in frontal meaningful hair density from 64 hairs/cm2 to 103 hairs/cm2. In the occipital region there was an increase in total hair density from 267 hairs/cm2 to 283 hairs/cm2 while meaningful hair density was not significantly changed from 239 hairs/cm2 to 246 hairs/cm2.

The error bars of the trichogram technique are shown in the figure for each measurement.

Conclusion

The topical application of **Trichogen III** resulted in significantly increased total hair density and meaningful hair density in the frontal region. It is proposed the the addition of cyclic AMP, ATP and Choline Theophyllinate will enhance the anti-androgenic action of Trichogen I and II.

4. Ineffective Topical Preparations applied to the scalp:

The following preparations were found to be ineffective in increasing hair density in common baldness in men:

a) Oestradiol Benzoate 0.01%
Medroxyprogesterone Acetate 0.01%
3, 3¯ 5 Triiodo-L-Thyronine Free Acid 20ug/3ml

b) Oestradiol Benzoate 0.1%
3, 3¯ 5 Triiodo-L-Thyronine Free Acid 20ug/3ml

c) Oestradiol Benzoate 0.1%
Medroxyprogesterone Acetate 0.1%

d) Oestradiol Benzoate 0.1%

e) Oestradiol Benzoate 0.01%

f) Medroxyprogesterone Acetate 0.1%

g) Medroxyprogesterone Acetate 0.01%

h) 3, 3¯ 5 Triiodo-L-Thyronine Free Acid 20ug/3ml

i) 3,3¯ 5 triiodo-D-Thyronine Free acid was not an effective substitute in any concentration for the -L- form.

j) Progesterone 0.1%

k) Progesterone 0.01%

None of the men who received topical treatment had any systemic side effects. All retained normal potency and beard growth. Three men who received the highest concentration of individual hormonal constituents (Oestradiol Benzoate 0.2%, Medroxyprogesterone Acetate 0.2%, 3, 3¯ 5 Triiodo-L-Thyronine Free Acid super-saturated solution) had full haematology, liver function tests, urea and electrolytes, endocrine profile and sperm counts carried out before, after 3 months and after 6 months of applying the preparation 2ml twice daily to the scalp without any significant change in the parameters measured. The patient who received this maximum concentration plus cyclic AMP free acid 0.1%; cyclic AMP sodium 0.05%, ATP magnesium 0.1%, Phentolamine 0.04% and Choline Theophyllinate 0.05% also had no change in potency nor beard growth and without any significant change in laboratory investigations and sperm count when the same parameters were checked before, after 3 months and after 6 months of applying the preparation, 2ml 4 times daily to the scalp. All patients noted a decrease in the greasiness of the hair and improved "condition" and cosmetic appearance. Three patients who had experienced superficial scalp tenderness and irritation prior to treatment noted the rapid alleviation of these symptoms within 1-2 days of begining topical treatment and for its duration.

5. Optimum formulation of preparation

From the above it is evident that Oestradiol Benzoate 0.1% alone or Medroxyprogesterone Acetate 0.1% alone or 3, 3¯ 5 Triiodo-L-Thyronine 20ug in 3ml of solution alone is not effective in producing hair growth in common baldness. Combinations of any two of the three are also not effective. 3, 3¯ 5 Triiodo-D-Thyronine free acid is not an effective substitute for the -L- form.

It appears necessary to combine Oestradiol Benzoate, Medroxyprogesterone Acetate with the Triiodothyronine to achieve therapeutic effect.

When the above combination was used but in reduced doses as Oestradiol Benzoate 0.01%, Medroxyprogesterone Acetate 0.01% while maintaining Triiodothyronine at 20ug/3ml there was no effect.

Thus:

1. The minimum effective dose of Oestradiol Benzoate and Medroxy-progesterone Acetate is between 0.01% and 0.1% when combined with Triiodothyronine at 20ug/3ml application.

The concentration of the main ingredients could be increased to Oestradiol Benzoate 0.2%, Medroxyprogesterone Acetate 0.2% and Triiodothyronine to the point of producing a super-saturated solution without causing local scalp irritation or producing systemic side effects. The solubility of these compounds in the solvent solution was maximal at room temperature.

Thus:

2. There would appear to be no added advantage in increasing the concentrations still further since it might be expected that the constituents would crystallise out on the scalp, becoming a powder.

Having regard for the known mechanism of action of steroids (and probably other hormones) cyclic AMP, ATP and other normally intra-cellular enzymes e.g. Cyclic GMP could be added to the formulation without impairing the effect or causing side effects and may produce added benefit in certain subjects. The concentrations of cyclic AMP and ATP were also maximal to produce a super-saturated solution at room temperature.

It was possible to add a vasodilator preparation, Phentolamine Mesylate to a concentration of 0.04% - 0.1% and probably higher. This preparation is a well recognised alpha- adrenergic blocker which may be expected to cause dilatation of peripheral capillaries in the scalp thereby increasing the blood supply to the hair follicle. When similar preparations are applied in solution in propylene glycol, industrial methylated spirit and water or in Ungentum Merck at 1% concentration as Minoxidil, hair growth can be achieved in patients with alopecia areata (see Topical Minoxidil in the Treatment of Alopecia Areata. Fenton D A, Wilkinson J D. British Medical Journal: 287, 1015-1017).

I propose that the combination of the topical antiandrogen preparation with an alpha-adrenergic receptor blocker or other vasodilator may enhance scalp hair growth in common baldness and also in alopecia areata by diminishing any additional inhibitory effects on hair growth by the common baldness process coexisting with alopecia areata. Three female patients with alopecia areata progressing to alopecia totalis capitis whom I have treated previously with cyclical antiandrogen therapy as:

Cyproterone Acetate 50mg daily for the first 10 days of each cycle.
Ethinyloestradiol 40ug daily for 21 days of each cycle

showed within 2-4 months the growth of fine downy hair over the scalp. Subsequently, this fell only to regrow again in six months. One patient had continued with treatment for 18 months and was growing terminal hair. Therefore, suppression of androgenic effects of endogenous hormones may potentiate the response to vasodilator substances.

Thus:

3. The combination of topical antiandrogen therapy with topical alpha-adrenergic receptor blocker or other vasodilator may produce an additional beneficial effect on scalp hair growth in common baldness as well as alopecia areata/totalis/universalis.

4. The combination of topical antiandrogen therapy as described with other known antiandrogens (e.g. cimetadine, azelaic acid) given topically or systemically, or with anabolic growth promoting substances e.g. growth hormone, may produce an additional beneficial effect on scalp hair growth in common baldness.

5. Topical antiandrogen therapy may be expected to produce increased hair growth (rate and/or density and/or fibre thickness) in apparently normal subjects and may be useful in the treatment of other conditions in which hair loss occurs e.g. following general viral, bacterial illness, post-pregnancy, pre-, peri-, post-menopausal women, post-irradiation; post-cytotoxic therapy, malnutrition, parasitic infections, metabolic disorders, infective conditions, following burns, physical or chemical injury to the scalp or in other conditions in which hair loss occurs.

6. Topical antiandrogen therapy may be used in patients with greasy hair and irritating scalp conditions and to improve the condition and appearance of existing hair.

7. Topical antiandrogen therapy may be in used in both male and female patients.

Table 1. Comparison between treatment group and control group in the treatment of male androgenic alopecia; following topical anti-androgen therapy.

TREATMENT GROUP: FRONTAL SITE.					OCCIPITAL SITE.			
	¶ THD		§ MHD		¶ THD		§ MHD	
Time Months	0	12	0	12	0	12	0	12
▲ P S	195	250	139	163	212	241	194	214
● J M	166	270	74	166	203	255	181	220
■ E D	155	205	74	79	210	222	192	192
★ A L	137	206	108	162				
CONTROL GROUP: FRONTAL SITE.					OCCIPITAL SITE.			
	¶ THD		§ MHD.		¶ THD		§ MHD	
Time Months	0	12	0	12	0	12	0	12
♯ R H	346	330	302	297				
◇ A C	313	308	305	295	310	306	303	297
♯ T B.	310	303	285	276	305	300	273	270
♯ G H	235	216	165	159	289	286	272	270
♯ J S	209	205	184	174	200	206	192	188
♯ F A	176	173	150	137	246	250	223	234

¶ THD - Hairs per cm^2

§ MHD - Hairs >40μm in diameter per cm^2

The above results suggest that it is the combination of the three essential active agents, viz. a thyroid hormone, an oestrogen and a non-oestrogenic anti-androgen, acting together in the region of the hair follicles that promotes hair growth. It will be appreciated, therefore, that it is not necessary to administer all three agents by the same route. Thus, for example, the thyroid hormone could be taken orally as a tablet, whilst the oestrogen and the non-oestrogenic anti-androgen could be applied topically as a lotion. Clearly, however, the oestrogen would normally not be administered to a male patient via the systemic route, because of adverse side effects.

Accordingly the present invention further provides a pack for a combination of pharmaceutical compositions for promoting scalp hair growth, which pack comprises at least one composition for systemic application and at least one composition for topical application, wherein each composition contains individually as ingredients a thyroid hormone, an oestrogen, a non-oestrogenic anti-androgen, or a mixture thereof, with the proviso that all three ingredients are present within the pack.

Also within the scope of the invention is the use of a combination of topical and systemic pharmaceutical compositions for promoting scalp hair growth wherein the combination includes as ingredients a thyroid hormone, an oestrogen and a non-oestrogenic anti-androgen.

CLAIMS:

1. A pharmaceutical composition for promoting scalp hair growth comprising, in combination, a thyroid hormone, an oestrogen and a non-oestrogenic anti-androgen.

2. A pharmaceutical composition as claimed in claim 1 wherein the thyroid hormone is thyroxine or triiodothyronine.

3. A pharmaceutical composition as claimed in claim 1 or claim 2 comprising as the anti-androgen a pharmaceutically acceptable derivative of medroxyprogesterone or cyproterone.

4. A pharmaceutical composition as claimed in claim 3 comprising as the anti-androgen medroxyprogesterone acetate or cyproterone acetate.

5. A pharmaceutical composition as claimed in any one of the preceding claims wherein the oestrogen is oestradiol or a pharmaceutically acceptable derivative thereof.

6. A pharmaceutical composition as claimed in any one of the preceding claims including at least one vasodilator, alpha-adrenergic blocker, anabolic growth-promoting agent, or "second messenger" hormone effector enzyme.

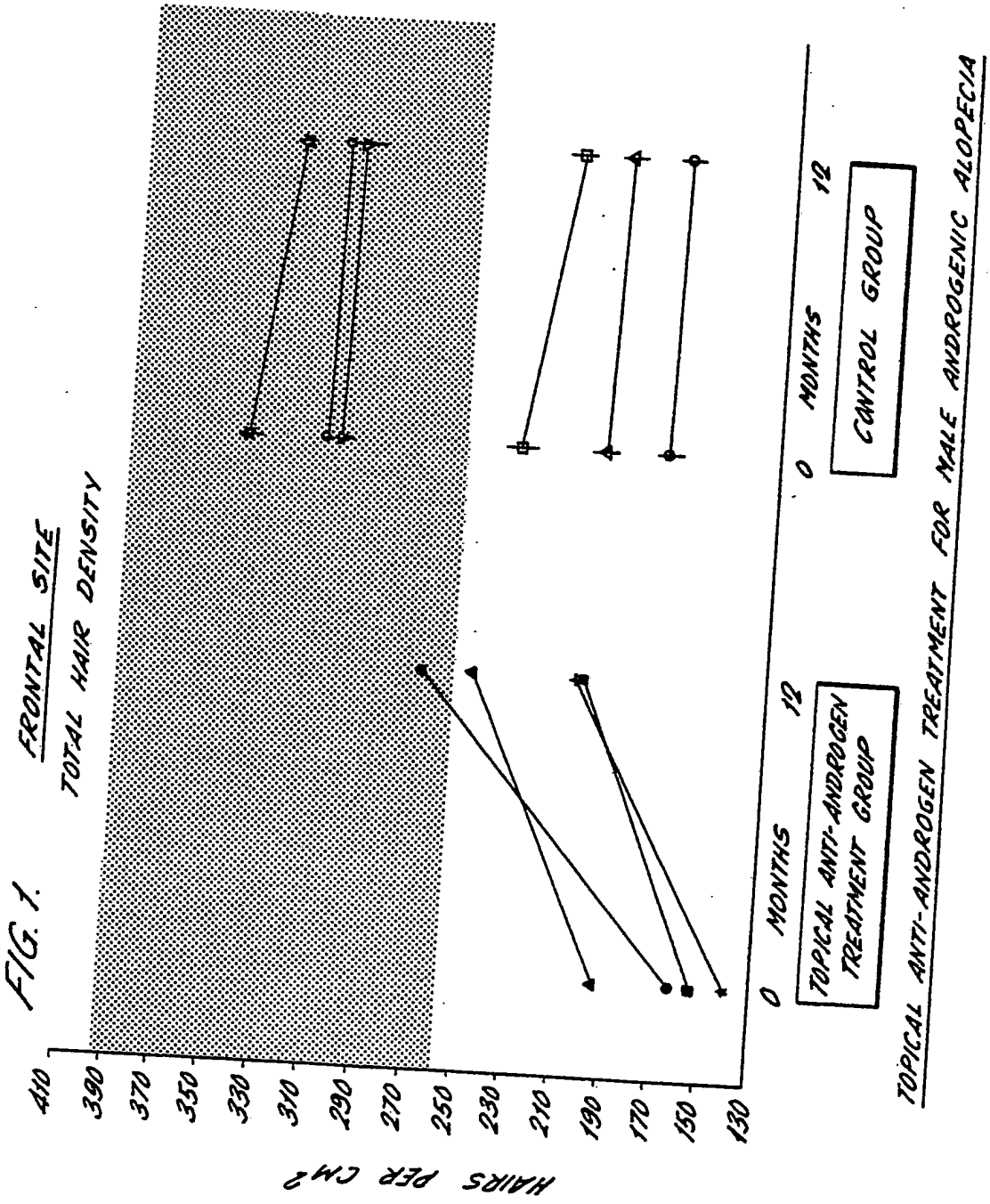
7. A pharmaceutical composition as claimed in any one of the preceding claims in the form of a cream, gel, ointment, paste, or lotion for topical application.

8. A pharmaceutical composition as claimed in any one of the preceding claims in a form for oral or parenteral administration.

9. A pack for a combination of pharmaceutical compositions for promoting scalp hair growth, which pack comprises at least one composition for systemic application and at least one composition for topical application, wherein each composition contains individually as ingredients a thyroid hormone, an oestrogen, a non-oestrogenic anti-androgen, or a mixture thereof, with the proviso that all three ingredients are present within the pack.

10. The use of a combination of topical and systemic pharmaceutical compositions for promoting scalp hair growth wherein the combination includes as ingredients a thyroid hormone, an oestrogen and a non-oestrogenic anti-androgen.

FIG. 1.



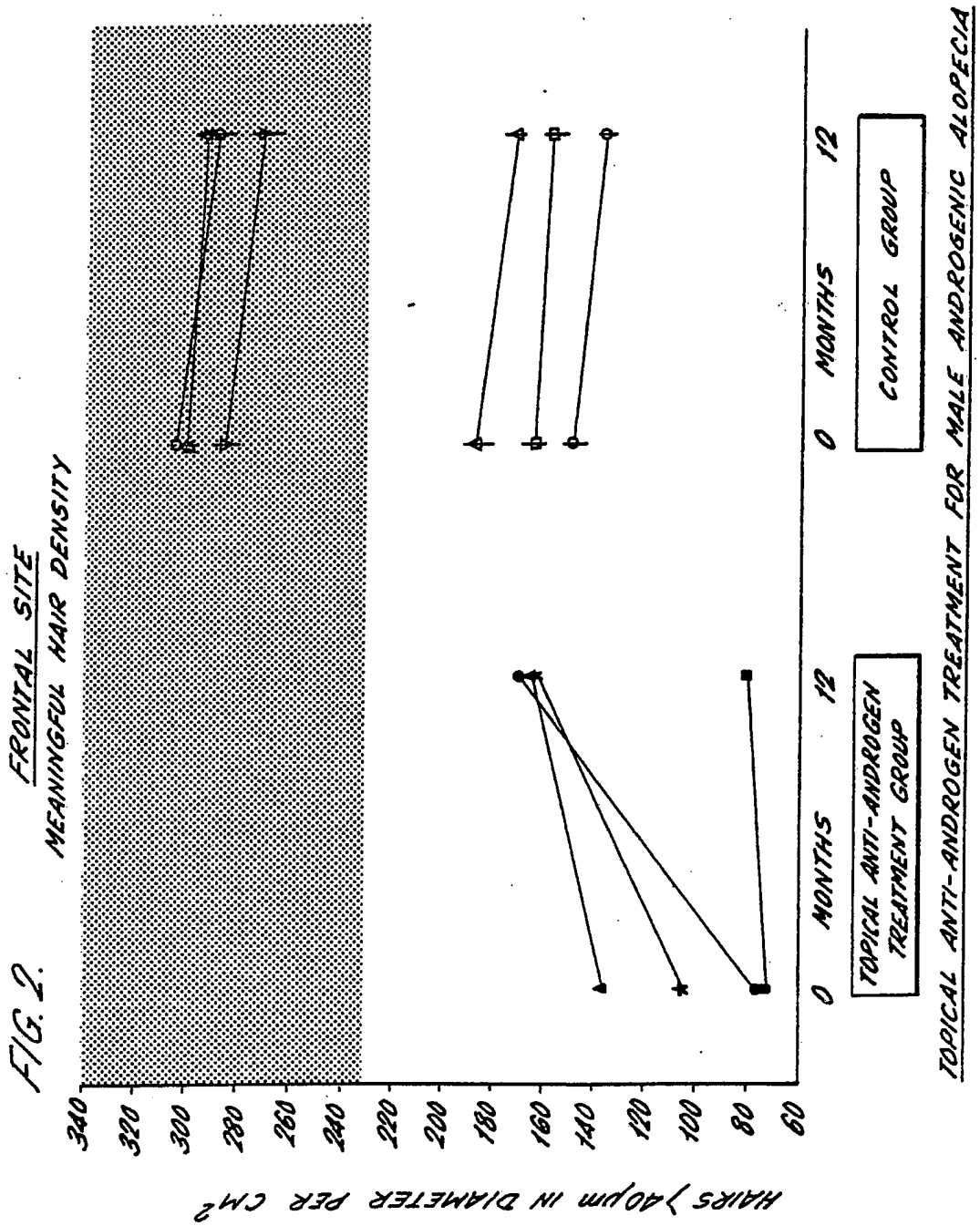
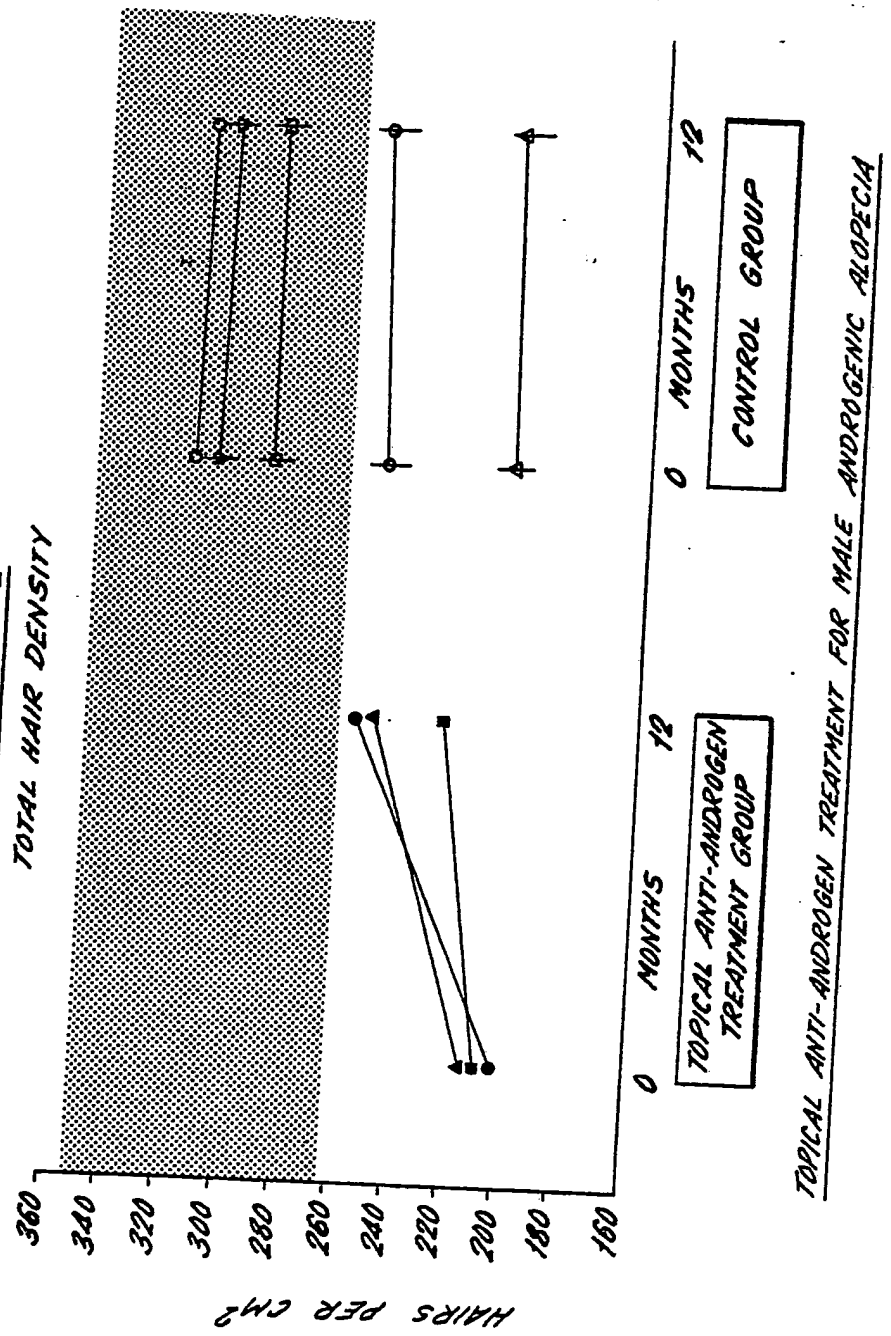


FIG. 2.

FIG. 3.



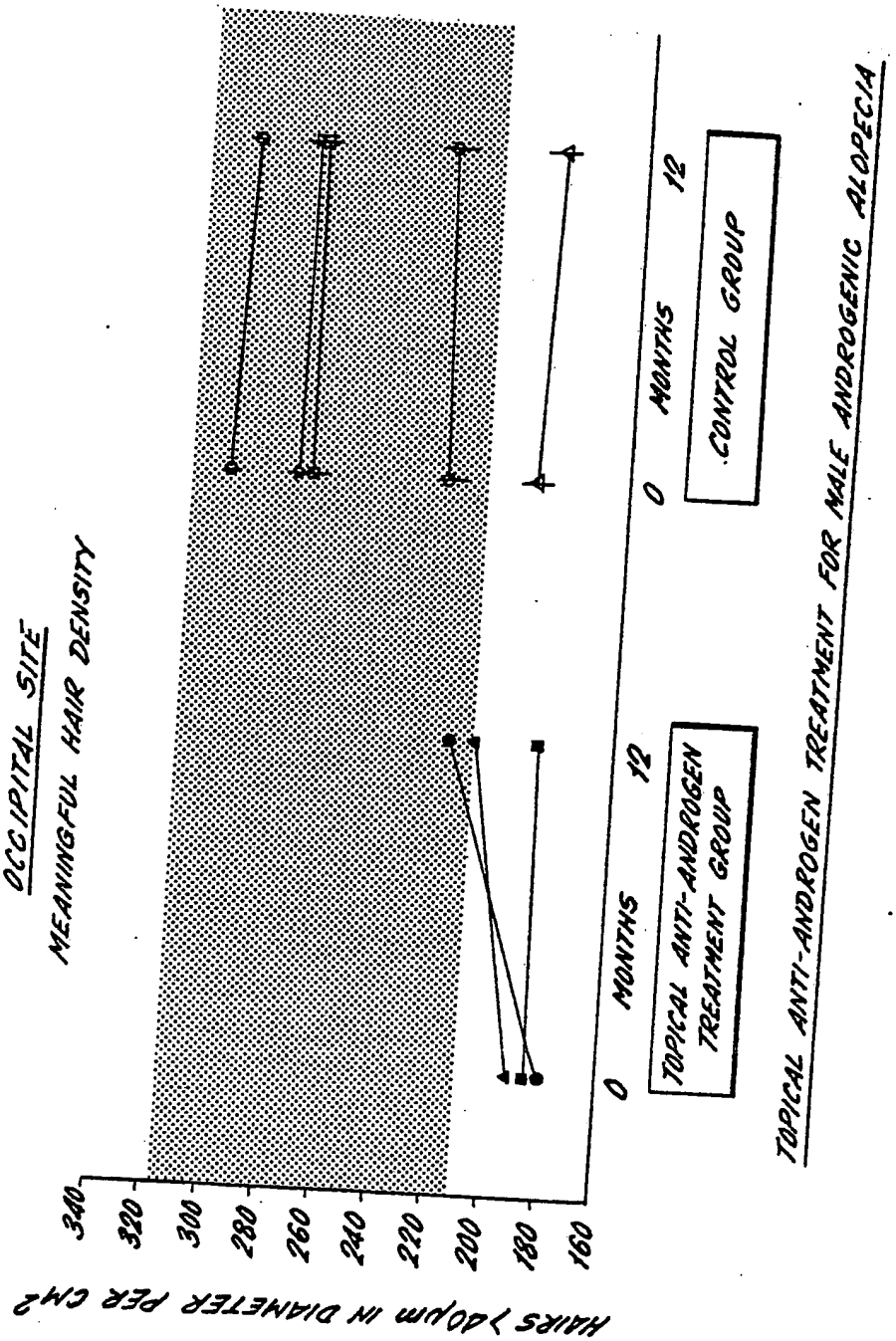
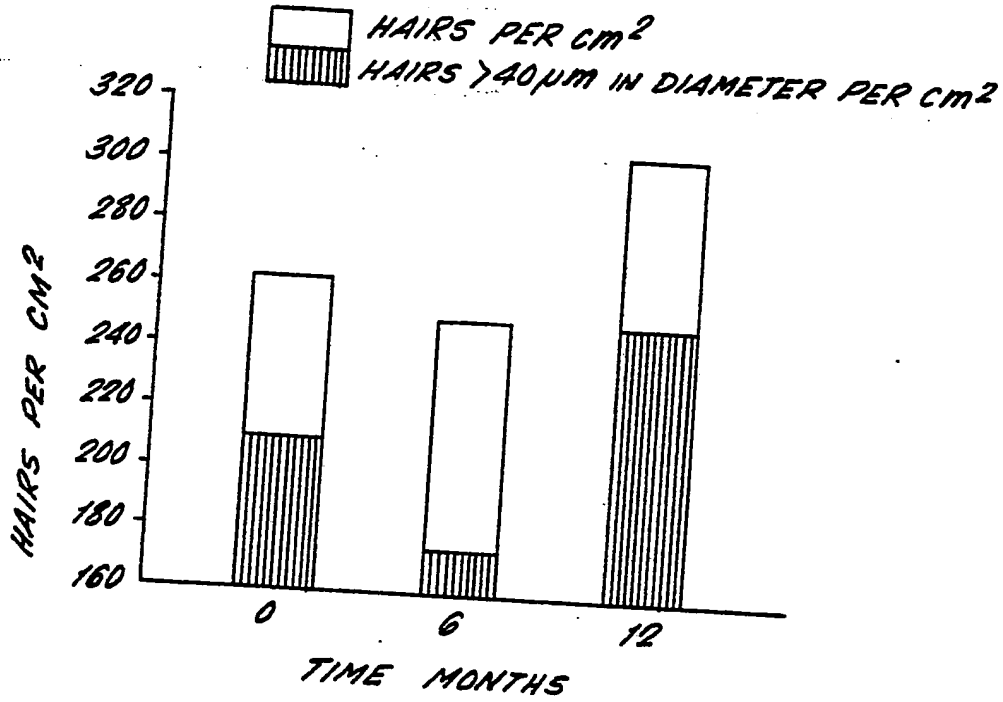
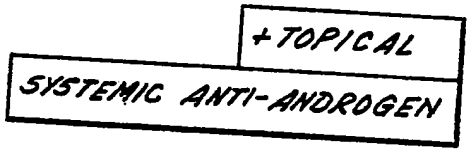


FIG. 4.
OCCIPITAL SITE
MEANINGFUL HAIR DENSITY

FIG. 5.

FRONTAL SITE





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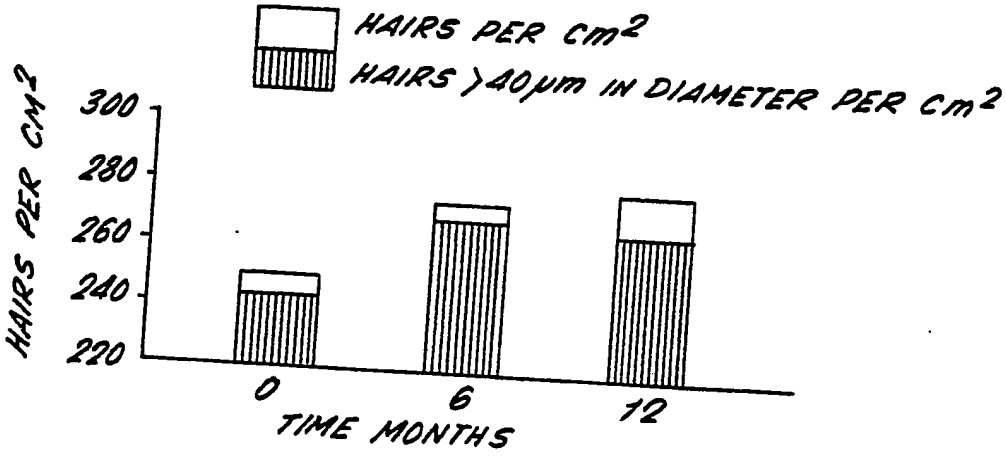
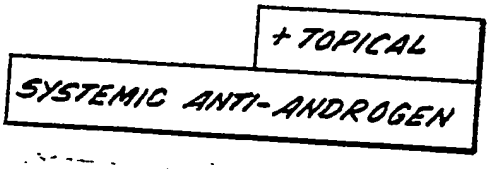




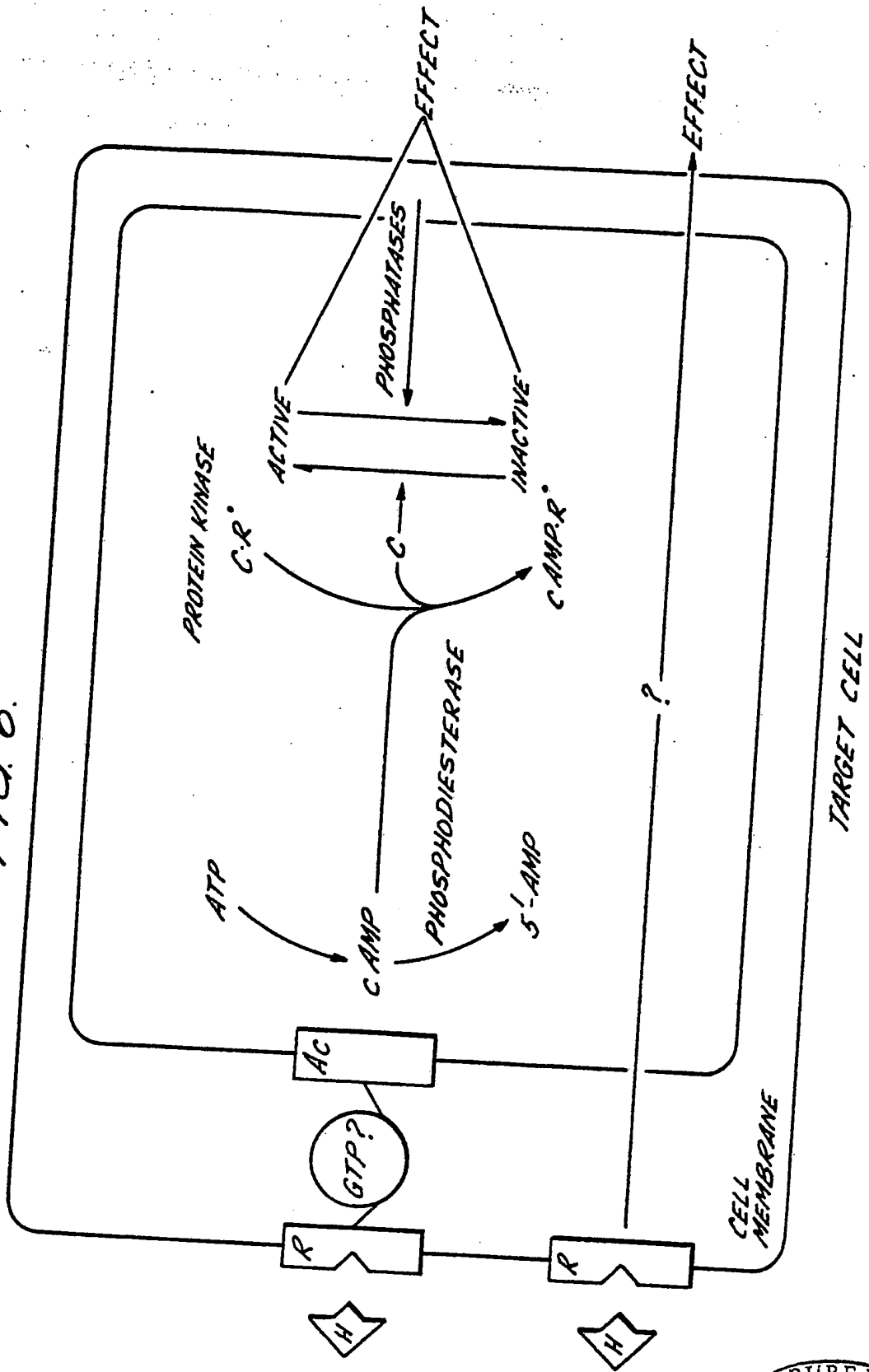
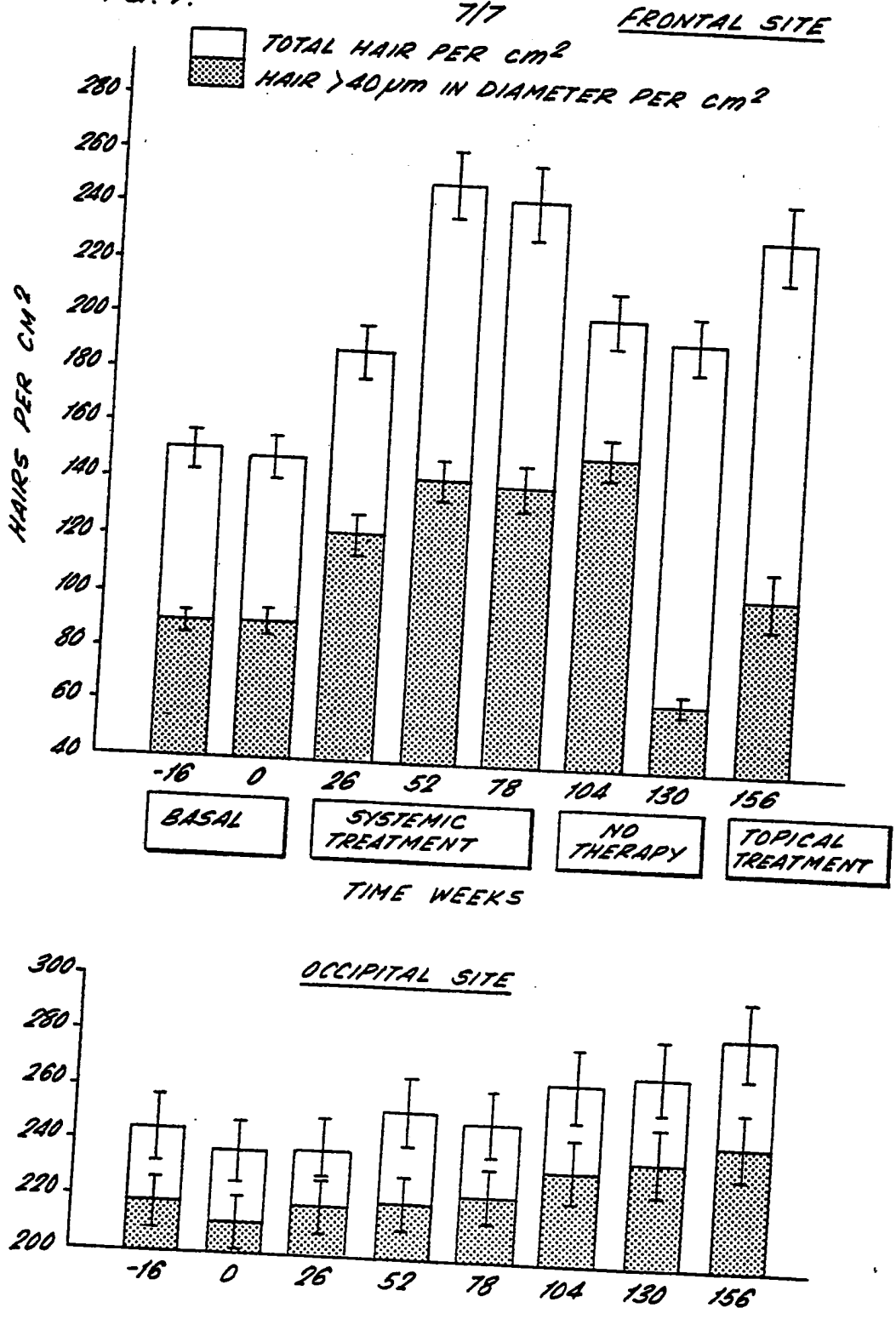


FIG 6.

FIG. 7.



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 84/00135

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3]: A 61 K 7/06

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[3]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	GB, A, 859546 (HELLBAUM) 25 January 1961 see the whole document, in particular page 2, example 2	1,2,5,7-9
A		3,4,6
	--	
Y	GB, A, 874368 (LUBOWE) 2 August 1961 see the whole document	1,2,5,7-9
A		3,4,6
	--	
A	FR, A, 2343474 (UNILEVER) 7 October 1977 see the whole document	3,4
	--	
A	EP, A, 0033164 (VON KISTOWSKI) 5 August 1981	
	--	
Y	FR, M, 6434 (GLASS) 9 December 1968 see the whole document	1,2,5,7-9
A		3,4,6
	------	

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
27th June 1984	20 JUIL. 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (October 1981)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 84/00135 (SA 6985)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 13/07/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A- 859546		None		
GB-A- 874368		None		
FR-A- 2343474	07/10/77	DE-A-	2710462	15/09/77
		AU-A-	2305177	14/09/78
		GB-A-	1570524	02/07/80
		CA-A-	1094456	27/01/81
		AU-B-	514909	05/03/81
		US-A-	4367227	04/01/83
		SE-A-	7702742	12/09/77
EP-A- 0033164	05/08/81	DE-A-	3003036	30/07/81
FR-M- 6434	04/11/68	BE-A-	877713	16/11/79

FURTHER INFORMATION CONTINUED FRO.1 THE SECOND SHEET

V. [x] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [x] Claim numbers 10, because they relate to subject matter [12] not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body
by surgery or therapy, as well as diagnostic methods (PCT Rule 39.1(iv)).

2. [ ] Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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International Bureau

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A1

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(33) Priority Country: GB

(71)(72) Applicant and Inventor: MORTIMER, Christopher, Harry [GB/GB]; 8 Park Square West, Regents Park, London NW1 4LJ (GB).

(74) Agent: BOULT, WADE & TENNANT; 27 Furnival Street, London EC4A 1PQ (GB).

(81) Designated States: AU, DK, JP, NO, US.

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF HAIR LOSS

(57) Abstract

A pharmaceutical composition for promoting scalp hair growth comprising, in combination, a thyroid hormone, an oestrogen and a non-oestrogenic anti-androgen. The preferred composition consists of an ointment or lotion containing triiodothyronine, oestradiol benzoate, and medroxyprogesterone acetate. Topical, systemic or a combination of topical and systemic application routes can be used for the three active agents.